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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,668	02/02/2004	Susan C. Wright	115-000420US	2158

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
11/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,668	WRIGHT ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 8/09/2007 in response to the previous Non-Final Office Action (4/09/2007) is acknowledged and has been entered.

Claims 1-19 are currently pending and under consideration.

Rejections Maintained:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 8 and 17 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. (WO 01/66689 A2, 2001, *of record*).

Tang et al. teach a composition comprising an isolated amino acid sequence, which has at least 99.8% sequence identity to the claimed SEQ ID NO: 4, comprising the instantly claimed amino acid sequence of SEQ ID NO: 6 and/or 7 and having SEQ ID NO: 4 (SEQ ID NO: 233 of WO publication, see below sequence comparison). With respect to the amino acid sequence, the WO publication teaches that the amino acids include, but are not limited to, both full length (comprising a signal sequence) and mature forms (without a signal sequence) (page 28, lines 19-20). Moreover, Tang et al. teach that the polypeptides may be operably linked to a targeting moiety such as an antibody which binds to a cell molecule (page 32, lines 1-14 and line 34 to page 33, line 25). For example, the WO publication teaches that the polypeptides may be operably linked to an antibody which specifically binds a target on pancreatic cells. In the instant case, the transitional phrase "comprises", which is synonymous with "including," "containing," or "characterized by," recited in the current claims is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., > Mars Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising,' the terms containing' and mixture' are open-ended.").<

Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.). Thus, in view of the transitional phrase, Tang et al. teach a composition comprising a portion of SEQ ID NO: 4, wherein the portion comprises SEQ ID NO: 6 or SEQ ID NO: 7. Moreover, although Tang et al. does not specifically teach that the polypeptide has activity chosen from DNA nuclease activity and cell killing activity, the claims are drawn to the product *per se* and inherently, such a polypeptide have activity chosen from DNA nuclease activity and cell killing activity. Thus, the claimed peptide appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

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Comparison between Tang's SEQ I DNO: 233 and claimed SEQ ID NO: 6
Novel human secretory protein, Seq ID No 233.
WO200166689-A2.
Tang YT,  Liu C,  Asundi V,  Xu C,  Wehrman T,  Ren F,  Ma Y,  Zhou P; Zhao
QA,  Yang Y,  Drmanac RT,  Zhang J,  Chen R,  Xue AJ,  Wang J;

1   KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKG 60
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
239 KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKG 298

61  IEKNLGIGKVSS 72
    ||||||||||||
299 IEKNLGIGKVSS 310

Comparison between Tang's SEQ I DNO: 233 and claimed SEQ ID NO: 7
Novel human secretory protein, Seq ID No 233.
WO200166689-A2.
Tang YT,  Liu C,  Asundi V,  Xu C,  Wehrman T,  Ren F,  Ma Y,  Zhou P; Zhao
QA,  Yang Y,  Drmanac RT,  Zhang J,  Chen R,  Xue AJ,  Wang J;
1   KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKG 60
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
239 KAKAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKG 298

61  IEKNLGIGKVSSFEEKMISDAIPELKASIKKGEDFVKTLK 100
    ||||||||||||||||||||||||||||||||||||||||
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299 IEKNLGIGKVSSFEEKMISDAIPELKASIKKGEDFVKTLK 338

Comparison between Tang's SEQ I DNO: 233 and claimed SEQ ID NO: 4
Novel human secretory protein, Seq ID No 233.
WO200166689-A2.
Tang YT, Liu C, Asundi V, Xu C, Wehrman T, Ren F, Ma Y, Zhou P; Zhao
QA, Yang Y, Drmanac RT, Zhang J, Chen R, Xue AJ, Wang J;

Query Match 99.8%; Score 1706; DB 4; Length 338;
Best Local Similarity 99.7%; Pred. No. 9.7e-168;
Matches 337; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

 1 MLSALARPASAALRRSFSTSAQNNAKVAVLGASGGIGQPLSLLLKNSPLVSRLTLYDIAH 60
   |||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||||
 1 MLSALARPVSAALRRSFSTSAQNNAKVAVLGASGGIGQPLSLLLKNSPLVSRLTLYDIAH 60

61 TPGVAADLSHIETKAAVKGYLGPEQLPDCLKGCDVVVIPAGVPRKPGMTRDDLFNTNATI 120
   ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
61 TPGVAADLSHIETKAAVKGYLGPEQLPDCLKGCDVVVIPAGVPRKPGMTRDDLFNTNATI 120

121 VATLTAACAQHCPEAMICVIANPVNSTIPITAEVFKKHGVYNPNKIFGVTTLDIVRANTF 180
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
121 VATLTAACAQHCPEAMICVIANPVNSTIPITAEVFKKHGVYNPNKIFGVTTLDIVRANTF 180

181 VAELKGLDPARVNVPVIGGHAGKTIIPLISQCTPKVDFPQDQLTALTGRIQEAGTEVVKA 240
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
181 VAELKGLDPARVNVPVIGGHAGKTIIPLISQCTPKVDFPQDQLTALTGRIQEAGTEVVKA 240

241 KAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIE 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
241 KAGAGSATLSMAYAGARFVFSLVDAMNGKEGVVECSFVKSQETECTYFSTPLLLGKKGIE 300

301 KNLGIGKVSSFEEKMISDAIPELKASIKKGEDFVKTLK 338
    ||||||||||||||||||||||||||||||||||||||
301 KNLGIGKVSSFEEKMISDAIPELKASIKKGEDFVKTLK 338
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In response to this rejection, Applicants assert that the in order for Tang to anticipate the instant invention, Tang et al. must teach a fragment of a mature MDH polypeptide, wherein the fragment comprises the SEQ ID NO: 6 portion of SEQ ID NO: 4 and exhibits cell killing or nuclease activity. However, Applicants assert that Tang et al., if anything, teaches a full-length mature MDH polypeptide and therefore all limitations of the claim are not found in the reference and it cannot anticipate the claimed invention. In particular, Applicants contend that it appears that the Examiner believes that the fact that the Tang sequence is not 100% identical to SEQ ID NO: 4 makes it a fragment and/or that Tang teaches a fragment and the remainder of the mature polypeptide is an optional unrecited element allowed by the term "comprising". However,

Applicants contend that while the Examiner is correct in asserting that the claim is written in open style and therefore does not exclude compositions containing the claimed sequence in combination with extra unrecited elements, a composition that includes additional unrecited elements must sill meet each and ever limitation of the claims including a fragment of a mature MDH polypeptide which is not taught in Tang. If anything, Applicants contend that Tang teaches a conservatively modified variant of SEQ I DNO: 4, e.g, a mature MDH polypeptide that does not anticipate the claimed invention. For example, Applicants contend that the specification describes MDH molecules as including variants of MDH of about the same molecule weight by with conservative substations such as a substitution of alanine for valine which is the same conservative substation sound between the Tang sequence and the mature MDH molecule described in the specification. Thus, Applicants assert that the sequence provided by the Examiner as anticipating the composition is a mature MDH sequence as defined in the present specification. Moreover, Applicants contend that Tang does not, in any way, teach or identify an MDH fragment as defined in the instant specification and presently claimed. For example, Applicants assert that the specification defines a fragment as being "from 4-50 or the entire amino acid sequence minus one amino acid residues" page 27, lines 4-5. Thus, Applicants assert that the entire sequence of Tang, e.g., a mature MDH variant, does not teach a fragment, e.g., a small part isolated from the whole or an entire sequence minus at least one residues. In addition, Applicants contend that while the Examiner correctly notes that SEQ ID NOs: 6 and 7 are contained within SEQ I DNO: 233, nothing in Tang identifies those sequences as having any importance, e.g, they are not isolated, and have not been identified as contributing to or having a particular activity when isolated from the mature polypeptide. Similarly, Applicants assert that even if the Examiner persists in call the sequence of Tang a fragment, it still cannot anticipate the claimed invention because it has not been shown to have the claimed cell killing and/or nuclease activity. In particular, Applicants assert that it is unlikely that the sequence taught by Tang would have the claimed activity as it is a conservatively modified variant of a protein that does not have the claimed activity in view of the surprising discovery that specific fragments of a mature MDH polypeptide have cell killing or nuclease activity, whereas mature MDH polypeptides do not. See, e.g., page 35, lines 15-22.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner recognizes that the instant claims are drawn to a composition comprising an isolated polypeptide fragment of a mature mitochondrial MDH polypeptide that comprises an amino acid sequence that comprises a portion of SEQ ID NO: 4, wherein said portion comprises SEQ ID NO: 6 and has activity selected from: DNA nuclease activation activity, and cell killing activity. Thus, the claims encompass an isolated fragment of a mature mitochondrial MDH polypeptide that comprises an amino acid sequence that comprises a portion of SEQ ID NO: 4, but does not appear to recite that the mature mitochondrial MDH polypeptide consists of SEQ ID NO: 4. Turning to the instant rejection, the Examiner recognizes that Tang et al. teaches a polypeptide consisting of 338 amino acid residues which is 98.7% similar to SEQ ID NO: 4, which comprises SEQ ID NO: 6 and SEQ ID NO: 7. In other words, the isolated polypeptide of Tang comprises an amino acid sequence that comprise a portion of SEQ ID NO: 3 from amino acids 10-338, wherein said portion comprises SEQ ID NO: 6 and/or 7. In particular, the Examiner recognizes that the isolated polypeptide of Tang comprises an amino acid sequence that comprises a portion of SEQ ID NO: 4there does not appear to be a "limit" on a mature mitochondrial (MDH) polypeptide, and therefore, there does not appear to be a limit to the fragment. Thus, while Applicants arguments appear to center around the opinion that the sequence taught by Tang et al. is a variant, e.g., conservative substitution of an alanine for valine, of SEQ ID NO: 4, the claims are not drawn to the isolated polypeptide fragment of SEQ ID NO: 4. Instead, in view of the specification, the claims encompass an isolated polypeptide fragment of a mature mitochondrial MDH polypeptide which encompass homologs of SEQ ID NO: 4 or 1 comprising the insertion of one or more amino acids. For example, the specification teaches that the terms "mitochondrial malate dehydrogenase" and "MDH" interchangeably refer to the exemplary amino acid sequence from human (SEQ ID NO: 4) and/or pig (SEQ ID NO: 1) and include equivalent fragments thereof, homologs thereof, and sequences that have about the same molecular weight thereto (page 33, lines 14-18). With regards to homologs, the specification teaches that the terms "variant" and "homolog" of a protein used herein refers to an amino acid sequence which differs by insertion, deletion and/or conservative substitution of one or more amino acids from the protein of which it is a variant (page 28, lines 18-21). Thus, in light of the specification, an amino acid sequence comprising an insertion, deletion and/or conservative substitution of one or more amino acids from SEQ ID NO: 4 or SEQ ID NO: 1 is a mitochondrial MDH polypeptide. Thus, the isolated polypeptide of Tang et al. is a fragment

of a homolog of SEQ ID NO: 4. Secondly, regarding Applicants assertions Tang et al. does not teach DNA nuclease activation activity and cell killing activity, the Examiner acknowledges, as stated above, that Tang et al. does not specifically teach that the polypeptide has activity chosen from DNA nuclease activity and cell killing activity. However, the Examiner recognizes that the claims are drawn to the product *per se* and inherently, such a polypeptide comprising SEQ ID NO: 6 or 7 as claimed would have this functional limitation. In the instant case, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Thirdly, regarding Applicants assertions that the instant inventors have surprisingly found that specific fragments of a mature MDH polypeptide have cell killing or nuclease activity where as mature MDH does not, the Examiner acknowledges this surprising discovery. However, the Examiner recognizes that mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (WO 01/66689, 2001, *of record*) in view of Wang et al. (Cancer Research 1991; 51: 3353-3355, *of record*).

Tang et al. teach, as applied to claims 1-5, 8 and 17 above, a composition comprising an isolated amino acid sequence, which has at least 99.8% sequence identity to the claimed SEQ ID NO: 4, comprising the instantly claimed amino acid sequence of SEQ ID NO: 6 and/or 7 and having SEQ ID NO: 4 (SEQ ID NO: 233 of WO publication, see below sequence comparison). With respect to the amino acid sequence, the WO publication teaches that the amino acids include, but are not limited to, both full length (comprising a signal sequence) and mature forms (without a signal sequence) (page 28, lines 19-20). Moreover, Tang et al. teach that the polypeptides may be operably linked to a targeting moiety such as an antibody which binds to a cell molecule, wherein the targeting moiety increases the biological activity of the polypeptide (page 32, lines 1-14 and line 34 to page 33, line 25). In addition, the WO document teaches that the polypeptide is useful for the treatment of cancers including, but not limited to, liver cancer (page 53, lines 5-29).

Tang et al. do not explicitly teach that the antibody binds to liver cancer cells, wherein the antibody is Hepama-1.

Wang et al. teach a Hepama-1 antibody toxin conjugate. Specifically, the reference teaches that the hepatoma cytotoxicity of the conjugate was 500-fold higher as compared to the free toxin.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was to combine the teachings of the references so as to attach the polypeptide as taught by Tang et al. with an antibody such as Hepama-1 in view of the Wang et al. One would have been motivated to do so because Wang et al. teaches that the hepatoma cytotoxicity of the conjugate was 500-fold higher as compared to the free toxin. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by attaching the polypeptide as taught by Tang et al. with an antibody such as Hepama-1 in view of the Wang et al, one would achieve a method for specific delivery and targeting of the polypeptide for the treatment of liver cancer.

In response to this rejection, Applicants assert that, as described above, Tang et al. does not teach each and every element of the claimed invention because it does not teach a fragment of a mature MDH molecule. Thus, Applicants contend that because the Examiner relies on Tang for this teaching and does not allege that Wang teaches a fragment of a mature MDH protein, this element of the claim is not met by the combination of references.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner recognizes that claims 9-16 are dependent from independent claim 3 which recites a composition comprising a conjugate that comprises an amino acid sequence comprising SEQ ID NO: 6, wherein said amino acid sequence is operably linked to a first molecule that specifically binds to a cell molecule, wherein said conjugate activity isselected from DNA nuclease activation activity and cell killing activity. As such, while the Examiner acknowledges Applicants arguments pertaining to Tang et al. not teaching a fragment of a mature MDH molecule, it is noted that the features upon which applicant relies (i.e., a fragment of a mature MDH molecule) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the Examiner recognizes that Tang et al. teach a conjugate comprising an amino sequence comprising SEQ ID NO: 6, wherein said amino acid sequence is operably linked to a first molecule that binds to a cell molecule. Secondly, Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claims 6-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (WO 01/66689, 2001, *of record*) in view of Sherman et al. (2002/0022027, 2002, *of record*).

Tang et al. teach, as applied to claims 1-5, 8 and 17 above, a composition comprising an isolated amino acid sequence, which has at least 99.8% sequence identity to the claimed SEQ ID NO: 4, comprising the instantly claimed amino acid sequence of SEQ ID NO: 6 and/or 7 and having SEQ ID NO: 4 (SEQ ID NO: 233 of WO publication, see below sequence comparison). With respect to the amino acid sequence, the WO publication teaches that the amino acids include,

but are not limited to, both full length (comprising a signal sequence) and mature forms (without a signal sequence) (page 28, lines 19-20). Moreover, Tang et al. teach that the polypeptides may be operably linked to a targeting moiety such as an antibody which binds to a cell molecule, wherein the targeting moiety increases the biological activity of the polypeptide (page 32, lines 1-14 and line 34 to page 33, line 25). In addition, the WO document teaches that the polypeptide is useful for the treatment of cancers including, but not limited to, liver cancer (page 53, lines 5-29).

Tang et al. do not explicitly teach that the polypeptide-antibody conjugate further comprises a cell internalization peptide and/or nuclear localization peptide.

Sherman et al. teach a composition comprising a Vpr polypeptide conjugated to a therapeutic molecule (ab). With regards to the Vpr peptide, the publication teaches that Vpr contains at least two nuclear localization signals and is capable of delivering molecules to the cell nucleus (page 1, 2nd column, paragraph 0006). With regards to the therapeutic molecule, Sherman et al. teach that the therapeutic molecules include, but are not limited to, polypeptides, polynucleotides and toxins (page 1, 1st column, paragraph 0007). Moreover, the publication teaches a method of killing a target cell and/or inhibiting cell proliferation or a target cell comprising administering a Vpr peptide conjugate or Vpr alone, wherein the Vpr conjugate is delivered into a cell and said cell is a cancer cell (abstract; page 1, 2nd column, paragraph 0008 and page 2, 1st column, paragraph 0010).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was to combine the teachings of the references so as to further attach a cell internalization/ nuclear localization peptide to the antibody-polypeptide conjugate as taught by Tang et al. in view of the Sherman et al.. One would have been motivated to do so because Sherman et al. teach that Vpr polypeptides conjugated to therapeutic molecules allows for the selective delivery of the therapeutic molecule within the cell, wherein the therapeutic molecule is released from the Vpr by protease cleavage of the Vpr conjugate. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering an antibody-polypeptide conjugate as taught by Tang et al. in view of Wang et al. which further comprises a cell internalization/ nuclear localization peptide, one would achieve a method for specific delivery and targeting the polypeptide for the treatment of cancer.

Secondly, each of the agents, e.g., the polypeptide and a Vpr polypeptide, have been individually taught in the prior art as being useful for the treatment of cancer. As such, the

strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Conclusion

Therefore, NO claim is allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF